Residents' Case Series

A 76 Year-Old Man with Anemia, Lymphadenopathy and Pericarditis.

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Case Report

76 year-old Chinese man presented to his primary care physician with a two-year history of progressive weight loss of 30 pounds and fatigue. The patient was referred for psychiatric evaluation, diagnosed with depression, and started on fluoxetine. He did not take any other medication or herbal remedies. He was then seen by another physician and found to have diffuse lymphadenopathy on physical examination. The patient was then scheduled for a right axillary lymph node biopsy. On the day of the procedure, he developed chest discomfort, and an EKG showed diffuse ST segment elevations consistent with pericarditis. Echocardiogram was performed and showed minimal pericardial effusion and ibuprofen was initiated. The patient then developed epistaxis and an ENT specialist performed a right- sided nasal packing. The patient was stabilized and underwent axillary lymph node biopsy. During the procedure he developed recurrent epitaxis and had nasal packing done again. In the recovery room, he was noted to be more anemic with decrease in his hemoglobin by 2 grams. He received packed red blood cell transfusion, and it was noted that his blood was difficult to type and crossmatch.

On physical examination after the lymph node biopsy, the patient was afebrile and normotensive. Skin examination revealed no malar rash, periungual telangiectasia, discoid lupus or alopecia areata. He had no obvious cutaneous vasculitis, synovitis or arthritis. The patient had scattered cervical and minimal axillary lymphadenopathy. There were no oral ulcers. Cardiac examination revealed no murmurs, rubs or gallop, and there was no hepatosplenomegaly. Neurological examination was normal.

Diagnostic data revealed: WBC of 4,100/cc (4,300-10,800/cc) with 11% lymphocytes and 17% monocytes. Hemoglobin was 10.1 g/dL (13-18 g/dL) following transfusion with relatively normal indices. Platelet count was 53,000/cc (130,000-400,000/cc). ESR was 122 mm/hr (0-20 mm/hr). BUN was 16 mg/dL (10-20mg/dL) and creatinine was 1.0 mg/dL (0.8-1.2 mg/dL). Calcium was 8.5 mg/dL (9-10.5 mg/dL). PT and PTT were normal. Albumin was 1.9 gm/dL (3.5-5.5 gm/dL) and globulin was 6 gm/dL (2.9-3.1 gm/dL). ANA was 1:2560 with homogenous pattern. Complement C3 was less than 25 mg/dL (55-120 mg/dL) and C4 was less than 10 mg/dL (20-50 mg/dL). Anti –double stranded DNA was positive at titer of 1:20. Anti-Smith/RNP was negative. ANCA was negative. Direct Coombs test was positive. Urinalysis showed 100 mg/dL of protein with no cells. Twenty-four-hour urine protein was 466 mg/24hr (0-150 mg/24hr). The tuberculin skin test was negative.

A Head CT scan showed fusiform aneurysm of the basilar artery with no other significant abnormalities. Chest, abdominal and pelvic CT scan showed bilateral pleural effusions and a moderate pericardial effusion with a small amount of ascites in the abdomen and pelvis. The renal ultrasound revealed calculus in the left kidney with minimal grade I hydronephrosis. There was an 8 mm calculus in the left ureter at the ureteropelvic junction. A bone scan was normal.

Bone marrow aspiration and biopsy revealed no abnormalities.

Lymph node biopsy revealed scattered secondary follicular cells with active germinal centers. The interfollicular tissue was composed of a polymorphous population of lymphocytes and plasma cells. There was background vascular proliferation. Very rare polykaryocytes were seen. No metastatic tumor, granulomas, or atypical lymphoid population.

Flow cytometric immunophenotypic of the lymph node showed predominantly peripheral T cells and a smaller population of polyclonal B cell.

Hospital Course

Patient was diagnosed with systemic lupus erythematosus and was started on intravenous methylprednisone 24 mg every 12 hours. His clinical status was markedly improved. The patient was then discharge with oral prednisone 60 mg/day.

Discussion

This is 76 year-old man who initially presented with generalized lymphadenopathy and then developed pericarditis. He fulfilled 4 criteria of the 1982 revised criteria for SLE[7] with serositis, a hematological disorder, high ANA titer, and positive anti-dsDNA antibodies. High ANA titers are found more often in SLE than other autoimmune diseases. The homogenous ANA pattern, which was present in this case, is common in patients with SLE but is not very specific. It can be seen in all the connective tissue disorders as well as in drug-induced LE. This patient had been on only fluoxetine. There has been no report of fluoxetine and drug-induced LE. The low C3 and C4 levels also support the diagnosis of SLE since severe RA, nephritis of non-SLE etiology, and liver disease were absent. In this patient, a positive ANA with depressed complement levels, in the absence of the above mentioned situations, are almost certain to be associated with SLE.

Lymphadenopathy has been reported to occur in 36 to 60 % of cases of SLE. However, lymphadenopathy as the first clinical manifestation, as in this case, is uncommon. In one series of 520 patients with SLE[1], enlargement of cervical lymph nodes was the first clinical manifestation in 2 % of the patients, and generalized lymphadenopathy had occurred at the time of diagnosis in only 1 %[1,2]. Therefore when this patient initially presented with lymphadenopathy, the other possible diagnoses had to be ruled out by either lymph node biopsy or fine needle aspiration[3]. The nodes in SLE usually are nontender and discrete, and they vary in size from few millimeters to 3 to 4 centimeters in diameter. Lymphadenopathy is more common in children than in adults and most marked among black patients. Patients with lymphadenopathy have more constitutional symptoms including fatigue, fever and weight loss, more cutaneous signs and symptoms, a high rate of hepatomegaly and splenomegaly, increased anti-dsDNA antibodies and decreased complement levels[5]. There is no difference in renal or central nervous system involvement between patients with lymphadenopathy and those without lymphadenopathy [5]. A meta-analysis showed that lymphadenopathy prevalence with late-onset SLE was lower

than in patients with early-onset SLE[11]. The histological findings of lupus lymphadenopathy are variable, ranging from follicular hyperplasia, edema and sinus histiocytosis in the early stages to confluent necrosis at late stages[8]. The characteristic finding in the lymph nodes of patients with SLE is a diffuse, reactive hyperplasia. There are hyperplastic germinal centers with plasmacytosis and variable number of immunoblasts in the interfollicular areas. In the necrotic areas and within the sinuses are occasional extracellular amorphous bodies, 5 to 12 microns in diameter, that stain intensely with hematoxylin. These "hematoxylin bodies" were first described by Ginzler and Fox in 1940[10]. It contains aggregates of DNA, immunoglobulins, and polysaccharides, and when present, they are considered to be characteristic of lupus lymphadenopathy. Although hematoxylin bodies can also occur in other diseases, such as progressive systemic sclerosis and rarely in patients with hyperglobulinemia, when clinical data is unavailable, the hematoxylin bodies are pathognomonic of SLE[2,3,8]. Cells resembling Reed-Sternberg morphology also have been described in patients with SLE[2]. Neutrophils, eosinophils, and granulomata are sparse[2,9,10]. These microscopic features serve to distinguish lupus lymphadenitis from other infections, immunologic, and vasculitis conditions[2,9]. The molecular genetic finding of oligoclonal TcR rearrangements may be a feature of SLE, or a concurrent but distinct disorder, such as the early phase of a lymphoid neoplasm[4].

The age and gender also have effects on clinical presentation and course in SLE. Most investigators report that female to male ratios with SLE after age 50 were decreased slightly to 8:1 from 10 to 15:1. Patients with drug-induced lupus are distinctly older and usually male, likely because commonly used drugs such as procainamide and hydralazine are widely used for conditions in people over age 50 years. SLE has no predilection for males who are older, but relative to younger patients (less than 50 years old), the numbers of men with SLE increase with age. One group found that the older SLE patient presents clinically more like the patient with drug-induced SLE than one with idiopathic disease[12]. This is because these patients have a low incidence of renal disease and, more prominent pleuropericardial and musculoskeletal symptoms[13]. Such older patients rarely have low complement levels and native DNA antibodies, which are opposite to the findings in this patient. The meta-analysis of older SLE patients revealed that serositis, interstitial pulmonary disease, anti La antibodies, and Sjogren's syndrome symptoms (secondary sicca) were commonly associated with the disease of the older age group. Alopecia, Raynaud's phenomenon, fever, lymphadenopathy, hypocomplementemia, and neuropsychiatric disease were uncommon in this group. However, the analysis showed no differences between older-onset and younger-onset SLE patients in the presence of nephritis, photosensitivity, oral ulcers, leucopenia, rheumatoid factor, and elevated anti-dsDNA antibodies[11]. Patients with onset of SLE after age of 50 years are usually considered to have a milder course and better prognosis than patients having the onset at younger age. Unlike in younger patients, where the major mortality is atherosclerosis, in older patients infection and perforated peptic ulcers were the most common cause of death. Thrombocytopenia was found in one study as the only independent clinical factor for a worse prognosis in SLE[15].

The effect of male sex on SLE also has been identified by many studies. One of the most striking characteristics of SLE is the higher prevalence among young women, which suggests a key role of sex hormones. Sex distribution before puberty and late in life does not show the marked preponderance of females seen in early adulthood. Additionally, the disease activity has been shown to be associated with pregnancy and postpartum. Furthermore, the association of SLE in males with Klinefelter syndrome is well known[16]. The murine model also showed the relation between autoimmunity and the sex hormones in females of some species; the *New Zealand White/Black* (AZW/NZB) *Fl hybrid* and the *MRL lpr* are strains in which females die at younger age then males. Although gender plays a role in the expression of SLE, it is not likely to be the etiology but rather an expression modifier. The hormonal metabolic studies data suggest that an increase in feminizing 16-hydroxylated estrogenic metabolites is found in SLE males, although no clinical findings of hyperestrogenism are found[17-21]. However, several male studies show no clinical difference between gender, and others have suggested that males have a more severe form of the disease[22]. One study from Singapore, which included 61 males (71% are Chinese) and 86 females, found that arthritis was significantly less common in men. Renal disease was the commonest clinical manifestation in this study. Furthermore arthritis and serositis were less common in contrast to the Caucasian patients. These findings provide evidence of differences between the genders in SLE and suggest that racial factors may affect clinical presentation[25]. One study of Latin American males found increased prevalence of renal disease, vascular thrombosis, and the presence of anti-dsDNA antibodies, as well as the use of moderate to high doses of corticosteroids, compared with female SLE patients. Although there was no difference in mortality from all causes, SLE-related mortality was higher in the male group in this study[16]. Another study found that male patients with SLE had increased rate of seizures and also showed a trend to progress to renal failure compared to females[23]. Increased incidence of thrombocytopenia and renal disease without other notable differences in clinical, laboratory, or serological parameters were found in one study including 52 males with SLE[24].

Clinical Implications

Clinicians should be aware that SLE patients might present with lymphadenopathy. Likewise, patients who fulfill the diagnostic criteria of SLE should be checked for any evidence of lymph node involvement. However, lymphadenopathy as the first clinical manifestation is uncommon. Therefore, when the patient presents with only lymphadenopathy, the other possible diagnoses have to be ruled out by lymph node biopsy.

Some studies have also found that SLE in elder patients may have different clinical presentations when compared to younger age patients. SLE is less common in males and may have different clinical implications compared to female patients.

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Continued on p. 89

"Residents' Case Series," continued from p. 81

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"Medical School Hotline," continued from p. 83

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